REMARKS

Withdrawal of the final rejection, entry of the above amendments and favorable reconsideration is respectfully requested in view of the following comments.

Upon entry of these amendments, claims 1, 4, 5, 6, 7, 8 and 11 will be pending, of which claims 1 and 4 are independent.

At the outset, Applicants wish to thank the Examiner for his courtesy and helpful discussion during the course of an interview held at the US PTO on February 4, 2003 (see the Examiner Interview Summary Record). Although no agreement was reached at the interview, the Examiner's suggestion to add additional features to claim 1 have been considered.

While the Applicants maintain that the previously examined claims are directed to patentable subject matter, nevertheless, in order to materially expedite prosecution, claim 1 now incorporates the ranges previously recited in claim 3 2 1. As such, the amended claim 1 does not raise any new issue requiring further consideration or search.

Claim 4 is rewritten in independent form, also incorporating the ranges from claims 2 and 3.

Claims 12 and 13 are cancelled although not the subject matter thereof.

Claim 11 is rejected under 35 USC §112, for failing to further limit claim 1. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 11 is directed an embodiment wherein the total concentration (condition ii) applies throughout the reaction. Claim 1 takes into account the embodiment wherein, for example, at the outset of the reaction, less than the entire amount of 6-APA is added at the beginning of the reaction, such as described on page 4, lines 15-18. Accordingly, the scope of claim 1 is broader than the scope of claim 11.

Claim 11 is not confusing and complies with 35 USC § 112, second paragraph. Withdrawal of this ground for rejection is respectfully requested.

Claims 1-8 and 11-13, all of the pending claims, stand rejected under 35 USC §103 as being obvious over WO 92 01061 (WO '061) taken with WO 95 03420 (WO '420) for the reasons of record and for the additional reasons set forth on pages 2-4. Applicants respectfully disagree and request reconsideration and withdrawal of this rejection for at least the following reasons.

The Examiner has complained that Applicants have not looked at WO '061 "as a whole." In particular, as explained by the Examiner during the interview, the basis of the rejection is that in view of the combined disclosures of an initial concentration of amino β-lactam (e.g., 6-APA) in the range of 50 to 750 mM and an initial concentration of acylating agent (e.g., phenylglycine derivative) above about 450 mM, any assertion of non-obviousness for amounts or ranges encompassed by such broad disclosure is effectively precluded. Applicants respectfully disagree.

First, as now recited in claim 1, the total concentration in the reaction mixture (which includes dissolved and non-dissolved ingredients) of 6-APA and ampicillin is greater than 300 mM. At the same time, the concentration of 6-APA dissolved in the reaction mixture is lower than 250 mM.

While the disclosure of WO '061 referred to above includes initial concentrations above and below 250 to 300 mM, nowhere is it suggested to or described how to, have a low solution concentration, i.e., dissolved amount, of 6-APA, lower than 250 mM, while at the same time having a higher total concentration of 6-APA (together with ampicillin), i.e., above 300 mM.

For example, if following the disclosure of WO '061 (as exemplified in all the working examples) using initial amounts of 6-APA below 250 mM, the total

concentration of 6-APA and ampicillin can never be more than 300 mM. Conversely, if, contrary to all of the working examples in WO '061, the practitioner determines to operate using a high initial concentration of 6-APA, there is no disclosure or assurance that the amount of dissolved 6-APA will not be greater than 250 mM. There is no disclosure in WO '061 which suggests maintaining a low concentration of dissolved 6-APA while, at the same time, having a high total concentration of 6-APA together with product ampicillin.

Additionally, while it may be possible to operate within the broad disclosure of WO '061 at a molar ratio of acylating agent to amino β-lactam, which is below 2.5, such possibility does not, without more, make the operation at such low molar ratio to be obvious. This is especially so in the absence of disclosure suggesting using sufficient low amounts of acylating agent to achieve molar ratios of acylating agent to 6-APA of not more than 2.5, coupled with all of the working examples for producing ampicillin, using molar ratios of 2.7 or higher. This was shown in Applicants' prior response and was also discussed during the recent interview.

In fact, for the embodiment of claim 4, reciting a molar ratio of not more than 2.0, the disclosure of WO '061 is further remote.

Regarding claim 5, WO '061 does not disclose a process wherein the 6-APA or the phenylglycine derivative is metered in partially over the course of the enzymatic acylation reaction. All that is described and emphasized is the importance of the initial starting amounts of the reactants. Therefore, one skilled in the art would not have been motivated to meter in the amino β-lactam and or the acylating agent in the method disclosed in WO '061. Claim 5 is separately patentable for this additional reason.

With regard to claim 7, for which the rejection relies on the disclosure of WO '420 as suggesting the use of D-phenylglycine amide.1 $2H_2SO_4$, this claim is at least patentable for the same reasons that claim 1 is patentable. That is, even assuming, without agreeing, that it would have been prima facie obvious to use D-phenylglycine amide.1 $2H_2SO_4$ as the acylating agent, it would still not have been obvious to carry out the process under the conditions set forth in claim 1.

The disclosure of WO '420 is also silent regarding a suggestion of operating at high total concentration of 6-APA and ampicillin and low concentration of dissolved 6-APA. WO '420 also does not disclose metering in during the course of the reaction either or both of 6-APA and the acylating agent. In fact, the WO '420 reference is directed to recovering the phenylglycine derivative from the reaction mixture and not to improving the reaction conversions. Therefore, WO '420 does not provide motivation to modify the process of WO '061. Still further, the WO '420 reference teaches that the concentrations of reactants used by this process are not critical (*see* page 1, lines 10-15). Thus the skilled artisan is afforded no reasonable expectation of success in obtaining better reaction conditions by the general reagent recovery technique described by this reference.

Therefore, no proper case of *prima facie* obviousness has been established in the record. Accordingly, Applicants request withdrawal of this rejection of claims 1-8 and 11-13, especially as applied to current claims 1, 4, 5 and 6-8 and 11.

CONCLUSION

In view of the above amendments to the claims and the foregoing remarks, the Applicants respectfully assert that all of the Examiner's objections and rejections have been overcome. Accordingly, early and favorable notice of allowance of the present application with claims 1, 4-8 and 11 is respectfully requested.

Respectfully submitted,

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APPENDIX

IN THE CLAIMS

Claims 1 and 4 are amended as follows:

1 (Four times Amended) A batch process for preparation of ampicillin comprising:

~~a)~~ acylating 6-aminopenicillanic acid (6-APA) with a phenylglycine derivative in the presence of an enzyme to form a reaction mixture;

wherein the process is carried out under the following conditions:

i) the total concentration in the reaction mixture of 6-APA and ampicillin combined is, substantially throughout the reaction, greater than ~~250~~ 300 mM;

ii) the concentration of dissolved 6-APA is lower than ~~300~~ 250 mM throughout the reaction; and

iii) the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.5.

4. (Four times amended) ~~Process according to claim 1, wherein~~ A batch process for preparation of ampicillin comprising.

acylating 6-aminopenicillanic acid (6-APA) with a phenylglycine derivative in the presence of an enzyme to form a reaction mixture;

wherein the process is carried out under the following conditions:

i) the total concentration in the reaction mixture of 6-APA and ampicillin combined is, substantially throughout the reaction, greater than 300 mM;

ii) the concentration of dissolved 6-APA is lower than 250 mM throughout the reaction; and

iii) the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.0.